REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks. Claims 1-71 and 98-104 are presently pending. By this amendment, claims 1, 4, 10, 36, 98, 102, 103 and 104 have been amended to more clearly recite specific aspects of the invention. Support for the amendments may be found throughout the claims and specification as originally filed, and the amendments do not constitute new matter. The amendments are not to be construed as acquiescence to any rejection and are made without prejudice to prosecution of any subject matter modified by amendment in a related divisional, continuation, or continuation-in-part application.

Objection to the Drawings

Applicants note the informalities indicated in PTO-948 and the requirement that corrected drawings be submitted within the timeframe for responding to the present action. Applicants submit that corrected drawings meeting the requirements of 37 C.F.R. § 1.85 are provided with the present amendment.

Information Disclosure Statement

The Action notes that the listing of references in the specification is not a proper information disclosure statement, and unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Applicants respectfully submit that all relevant references were cited in the information disclosure statement submitted March 23, 2001, the supplemental information disclosure statement submitted June 22, 2001, and the second supplemental information disclosure statement submitted February 5, 2002, which have been initialed and, thus, made of record in the instant application.

Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1-71 and 98-104 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way a to enable one skilled in the art to make and/or use the invention. More specifically, the Action alleges that the claims are directed to a device having utility solely in gene therapy, but the skilled artisan would not be able to use the claimed device without engaging in undue experimentation to devise a method of treatment.

Applicants respectfully traverse this basis of rejection and submit that the instant specification fully enables the skilled artisan to make and use the claimed invention.

As an initial matter, Applicants submit that the specification clearly describes uses of the claimed invention in addition to gene therapy. For example, the claimed invention may be used for birth control, and patients may be treated according to the invention with peptide hormones that affect fertility (page 46, lines 16-19). In yet another example, the claimed invention may be used to provide a structural support for tissue or organ reconstruction or enhancement, and bioactive agents having anti-inflammatory activities may be provided systemically according to the invention to curtail undesirable immune responses to the implant (page 46, lines 20-24). Furthermore, Applicants submit that the specification clearly contemplates using the claimed invention for providing polypeptides, *e.g.,* therapeutic polypeptides, to a patient in contexts other than to replace or supplement a polypeptide that is not being produced at normal levels in a patient. Applicants submit that the skilled artisan would readily be able to make and use the invention for these purposes based upon the teachings of the instant application and general knowledge in the art, so the specification is fully enabling for such uses of the claimed invention.

Applicants further submit that the underlying basis of this rejection appears to be that the specification does not enable the use of the claimed device due to a lack of evidence demonstrating its usefulness in human gene therapy. If this is true, the Examiner is asserting that the claimed invention lacks *in vivo* utility. Although this rejection is not made under 35 U.S.C. § 101, the legal standard to be applied is the same. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995) (Although the Examiner rejected pharmaceutical compositions based on § 112, a § 101 rejection for lack of utility would also have been proper.) Applicants submit that to the extent this

rejection is based upon a lack of evidence demonstrating therapeutic effectiveness in humans, the rejection is inappropriate, as a demonstration of therapeutic efficacy is not required to obtain a patent. Applicants note that the Patent Office has explicitly adopted the position established by the courts that an applicant does not have to provide actual evidence of success in treating humans where such utility is asserted. M.P.E.P. § 2107.03(I). In addition, the M.P.E.P. enunciates the Patent Office's standard for establishing therapeutic utility when stating that "if reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process." M.P.E.P. § 2107.03(III). In *no* case has a Federal court required an applicant to support an asserted utility with data from human clinical trials. Moreover, in *In re Brana*, the Federal Circuit emphatically rejected the PTO position that human clinical testing is necessary to establish practical utility for an antitumor agent. 51 F.3d 1560. Importantly, the court noted, citing *In re Krimmel*, 130 U.S.P.Q. 205 (C.C.P.A. 1961):

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, **even though it may eventually appear that the compound is without value in the treatment of humans**. (Emphasis added)

Here, the situation is analogous. The Applicants have demonstrated a device and method for the effective systemic delivery of a bioactive agent; whether the device will eventually have commercial value in the treatment of humans is not a relevant inquiry to determine patentability. Although the Action asserts that the instant application fails to provide a working example of expression of a therapeutic protein, Applicants submit that such a demonstration is not necessary to establish enablement for such a use. Contrary to the Action's assertions regarding lack of examples demonstrating delivery of genes encoding therapeutic products, there is no requirement that Applicants provide data for every gene encoding a protein or therapeutic protein that may be delivered by the claimed methods (see *Amgen v. Chugai and Genetics Institute*, 927 F.2d 1200 (Fed. Cir. 1991)). Moreover, it is well established that examples are not required for an enabling disclosure. *In re Robins*, 166 U.S.P.Q. 552 (C.C.P.A.

1970); *In re Borkowski*, 164 U.S.P.Q. 642 (C.C.P.A. 1970). The first paragraph of § 112 requires nothing more than objective enablement, which Applicants have provided. In this regard, the PTO explicitly accepts the use of prophetic disclosures. Thus, the examples included in the present application should be considered as supportive of enablement, not a detriment, as apparently argued by the Examiner.

In further support of the contention that the claims are not enabled, the Action cites numerous references allegedly disclosing problems with gene therapy. While these references represent sweeping generalizations of gene therapy, Applicants note that these references only tell one side of the story. In this regard, to date there are dozens of clinical trials in the U.S., and many more around the world, that involve the use of gene therapy. It is wholly improper and unfair to focus solely upon the technical hurdles faced by some in the field while ignoring the successes.

For example, Applicants draw the Examiner's attention to the results of gene therapy to treat severe combined immunodeficiency. Blaese *et al.*, *Science 270*:475-480 (1995). In this study, two children with a genetic defect in production of adenosine deaminase (ADA) were treated with a cloned ADA gene inserted into a retroviral vector. More than one year after this treatment both patients continued to display significant improvement in their immune system function. The results of this gene therapy treatment were markedly superior to those produced earlier by alternative treatment means.

In a cancer context, Roth *et al.*, *Nature Medicine 2*(9):985-991 (1996), have shown that a recombinant retroviral vector targets tumor cells *in vivo*. Moreover, this vector, which encodes the tumor suppresser p53, provided a sufficient level of p53 expression such that apoptosis, or programmed cell death, was triggered in these cells. Accordingly, retrovirus gene therapy was accomplished *in vivo*. Most recently, with respect to X-linked severe combined immunodeficiency (*i.e.*, SCID-X1), Cavazzana-Calvo *et al.*, *Science 288*:669-672 (2000), have demonstrated full correction of disease phenotype in patients treated by gene therapy protocols. Further, Kay *et al.*, *Nature Genetics 24*:257-261 (2000), have demonstrated therapeutic efficacy in the treatment of Haemophilia B with AAV vectors carrying the gene that encodes factor IX.

The successes of gene therapy are in no way limited to only these examples. According to a recent review article,

> Probably the most remarkable conclusion drawn from the human trials is that human gene transfer is indeed feasible ... [and] most studies have shown that genes can be transferred to humans whether the strategy is *ex vivo* or *in vivo*, and that all vector types function as intended. Taken together, the evidence is overwhelming, with successful human gene transfer having been demonstrated in 28 *ex vivo* and 10 *in vivo* studies. Crystal, *Science 270*:404, 405 (1995).

Regarding the Action's allegation that use of the claimed devices would require undue experimentation, Applicants submit that use of the claimed devices would require merely routine testing and not undue experimentation. Applicants note that for enablement purposes, a specification need not teach what is well known in the art. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). Moreover, some amount of experimentation is not fatal as long as the amount is not undue. *Id.* For the present claims, no undue experimentation is required, because the specification provides sufficient guidance to allow one of ordinary skill in the art to make and use the claimed devices for the systemic delivery of a bioactive agent. More specifically, the specification details how to construct and combine each element of the claimed devices, including the biocompatible substance and the nucleic acid molecules. Furthermore, the specification clearly demonstrates effective cellular infiltration and gene expression using the claimed device (*see* Examples 1 and 2). Applicants submit that the production and optimization of the claimed devices would, therefore, only require merely routine optimization and testing, such as could be determined and performed by the skilled artisan using a variety of known methods.

In light of these remarks, Applicants respectfully submit that the claims are fully enabled by the instant application and request that the Examiner withdraw this ground of rejection.

Rejection Under 35 U.S.C. § 112, First Paragraph, Written Description

Claim 10 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time the application was filed. More specifically, the Action alleges that the claim encompasses a genus of bioreactors comprising any and all mutated FGF-2 molecules possessing certain functional characteristics, but the specification fails to provide sufficient description of a representative number of species and fails to disclose sufficient relevant identifying characteristics of mutated FGF-2 molecules to support the claimed genus. Rather, the Action asserts that only the bioreactor comprising specific mutated FGF-2 polypeptides disclosed in the instant specification meets the written description requirement.

Applicants respectfully traverse this rejection and submit that the specification provides adequate written description for the entire genus of bioreactors comprising mutated FGF-2 polypeptides. Under the Examination Guidelines set forth by the Patent and Trademark Office, the written description requirement for a claimed genus may be satisfied by the description of a representative number of species or the disclosure of relevant, identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112, ¶1, "Written Description" Requirement, 66 Fed. Reg. 1099, at 1106. Applicants submit that the instant application meets both criteria.

First, contrary to the position adopted by the Action, Applicants submit that the instant specification describes a representative number of claimed species by providing the sequence of two mutant FGF-2 polypeptides having the identified characteristics. Applicants note that the description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species the genus embraces. *Id.* Applicants submit that by providing a reference sequence and disclosing the sequence of two distinct species within the claimed genus, the specification adequately describes a representative number of mutant FGF-2 polypeptides, since one skilled in the art would readily identify a mutant FGF-2 sequence based upon the descriptions provided in the instant application.

In addition, Applicants submit that the instant specification discloses sufficient identifying characteristics for mutant FGF-2 polypeptides that are common to the genus since it provides both a reference sequence and functional characteristics that may be used to identify a mutant FGF-2 of the invention. Moreover, Applicants submit that the instant application satisfies both the possession and notice functions of the written description requirement, since one of skill in the art would clearly be able to recognize and identify a claimed bioreactor comprising a mutant FGF-2 based upon the instant specification and would also understand that Applicants had possession of said bioreactors at the time the application was filed.

However, to expedite prosecution of the instant application and without acquiescence to this basis of rejection, Applicants have amended claim 10 so that it is directed to FGF-2 mutants in which one or more cysteine residues are substituted by a serine residue. Applicants submit that mutant FGF-2 polypeptides having these characteristics are clearly described in the instant specification and U.S. Patent No. 5,223,483, which is incorporated by reference in the instant application (page 28, lines 13-18). Accordingly, Applicants respectfully request that this basis of rejection is reconsidered and withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 5, 6, 8-10, 12, 13, 36 and 102 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Action alleges that claims 5 and 6 are indefinite in their recitation of "PDGF family members," claims 8, 9 and 10 are indefinite in their recitation of "FGF family members," and claims 12 and 13 are indefinite in their recitation of "TGF family members," since there is no antecedant basis for these terms in claim 4.

Applicants respectfully traverse this basis of rejection and submit that the skilled artisan would understand that the term "family members" at the end of claim 4 refers to all of the growth factors recited in the claim. Nonetheless, to provide additional clarity, Applicants have amended claim 4 to specifically recite "PDGF family members," "FGF family members," and "TGF family members," as suggested by the Examiner, thereby obviating this basis of rejection.

In addition, the Action alleges that claim 36 is indefinite in its recitation of "anticoagulant," since there in no antecedant basis for "anticoagulant" in claim 35. Applicants appreciate the Examiner's noting that Applicants intended for claim 36 to recite "coagulant" and have amended the claim accordingly, thereby obviating this basis of rejection.

The Action further alleges that claim 102 is indefinite in its recitation of an optional limitation, since it is unclear how the claim further limits the base claim, claim 98. Applicants have amended claim 102, as suggested by the Examiner, so that the limitation is stated in definite terms, thereby obviating this basis of rejection.

Applicants respectfully submit that the claims meet the requirements of 35 U.S.C. § 112, second paragraph, and request that these bases of rejection be reconsidered and withdrawn in light of these amendments and remarks.

Rejections Under 35 U.S.C. § 102

Claims 1-6, 8, 9, 11-13, 23-26, 39-43, 49-55, 57-67, 69 and 98-104 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by WO 95/22611 (the '611 application). More specifically, the Action alleges that the claims are directed to an *in situ* bioreactor comprising (1) a first nucleic acid molecule encoding a cell growth stimulating agent, (2) a

second nucleic acid molecule encoding a bioactive agent, and (3) a biocompatible substance capable of cellular infiltration. The Action further alleges that the '611 application discloses each of these elements and teaches that they can be combined and concludes that the '611 application, thus, teaches the *in situ* bioreactor of the instant application.

Similarly, claims 1-9, 11-15, 23-26, 39-43, 49-55, 57-67, 69, 70 and 98-104 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 5,962,427 (the '427 patent). The Action alleges that the '427 patent teaches each of the elements of the claimed *in situ* bioreactor and the combination of these elements, thereby teaching the *in situ* bioreactor of the instant application.

Applicants respectfully traverse this basis of rejection and submit that the claims are not anticipated by the cited references. Applicants submit that these references fail to disclose or describe an *in situ* bioreactor adapted for the systemic delivery of bioactive agents, as presently claimed. Applicants further submit that the cited references provide absolutely no description or recognition that devices for the introduction of DNA into mammalian cells can be adapted or used for the systemic delivery of a bioactive agent.

Applicants submit that the '611 application is directed to devices for the localized introduction of nucleic acids into bone cells for the purpose of promoting bone growth, repair and regeneration. As described beginning on page 8, line 15, the device of the '611 application is used to direct expression of a nucleic acid in bone cells for the purpose of altering the phenotype of the bone cells in which the nucleic acid is expressed. The '611 application further teaches that the device is used to introduce nucleic acids into bone ells and tissues "at the area of bone fracture or damage that one desires to treat" (page 10, lines 27-30). Furthermore, in describing how to use the device, the '611 application states that it must be placed in contact with the site in the body in which one wishes to promote bone growth. Accordingly, Applicants submit that the '611 application merely describes a device for the localized delivery of an agent. The '611 application provides absolutely no description of a device adapted for the systemic delivery of a bioactive agent.

Applicants further submit that the '427 patent is directed to a device implanted into a wound site that facilitates the transfer of DNA into mammalian repair cells localized at the

wound site for the purpose of expressing a therapeutic protein that promotes healing of the wound (column 2, lines 21-32). Thus, the '427 patent is also clearly directed to a device for the localized delivery of a therapeutic agent.

In addition, Applicants note that a "bioactive agent," as defined in the instant application, refers to any polypeptide based substance whose systemic availability over a period of time is desired or whose targeted delivery is effectuated through the circulation (page 8, lines 10-14). The '611 application and the '427 patent do not require that the agent is systemically available and do not require that targeted delivery is effectuated through the circulation. Rather, according to these references, delivery is effectuated locally into cells at the site of the implanted device. Indeed, the '427 patent actually teaches away from the presently claimed invention, since it describes numerous disadvantages associated with the systemic delivery of therapeutic proteins (column 2, line 65 - column 3, line 10). Thus, Applicants submit that these references fail to teach each element of the claimed invention.

Furthermore, without acquiescing to these bases of rejection and for the sole purpose of providing additional clarity, Applicants note that claims 1, 98, 103 and 104 have been amended to explicitly describe the claimed devices and kits as being adapted for system delivery of a bioactive agent in the body of the claims. Applicants submit that these amendments are fully supported by the instant application (*e.g.*, page 3, lines 21-23). Applicants further submit that the requirement that the claimed devices are adapted for systemic delivery has been consistently recognized by the courts as a limitation that must be considered in determining patentability. See, *e.g., Ex Parte Conner,* 215 U.S.P.Q. 384 (Pat. & Tr. Office Bd. App. 1981). Applicants submit that both references fail to disclose a device for the systemic delivery of a bioactive agent, and, accordingly, both references fail to anticipate the claimed invention. Applicants respectfully request that these bases of rejection be reconsidered and withdrawn in light of these amendments and remarks.

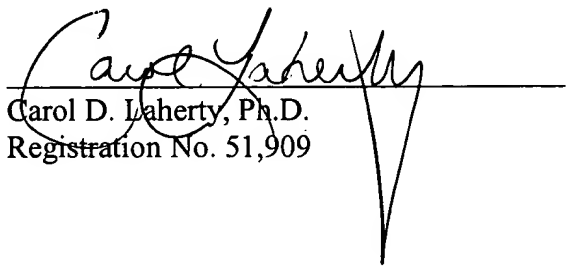
The Commissioner is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are now believed allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

Glenn Pierce et al.

SEED Intellectual Property Law Group PLLC



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